Otsuka Pharmaceutical Development & Commercialization, Inc.

Investigational Medicinal Product

Centanafadine (EB-1020)

CLINICAL PROTOCOL

Protocol Title: A Phase 1, Open-label Trial to Determine the Dose Proportionality and Multiple Dose Pharmacokinetics of Centanafadine Once Daily Extended-release Oral Capsules in Healthy Adults

Protocol Lay Person Short Title: A Study to Test How Different Doses of Centanafadine Given for Multiple Days are Taken up in the Body

Protocol No. 405-201-00154
IND No. 119361

CONFIDENTIAL — PROPRIETARY INFORMATION

Drug Development Phase:	1
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List of Abbreviations

Abbreviation	Definition
5-HT	serotonin
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
anti-HCV	hepatitis C antibodies
APMP	Abuse Potential Monitoring Process
AST	aspartate aminotransferase
AUC_{τ}	area under the plasma concentration-time curve over the dosing interval at steady state
BMI	body mass index
C_{24h}	concentration of drug in plasma at 24 hours
CL_{ss}/F	apparent clearance at steady state
CRO	Clinical Research Organization
$C_{ss,max}$	maximum (or peak) serum concentration at steady state
C-SSRS	Columbia-Suicide Severity Rating Scale
DA	dopamine
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ESAM	Event Subject to Additional Monitoring
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practice
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	identifier
IMP	investigational medicinal product
IND	Investigational New Drug
IR	immediate-release
IRB	institutional review board
IRE	immediately reportable event
MDD	major depressive disorder
MedDRA	Medical Dictionary for Regulatory Activities
MHI	medication handling irregularity
NE	norepinephrine
PK	pharmacokinetic(s)

Abbreviation	Definition
POCBP	participants of childbearing potential
PORP	participants of reproductive potential
PQC	Product Quality Complaint
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SR	sustained-release
$t_{1/2,z}$	terminal-phase elimination half-life
TDD	total daily dose
TEAE	treatment-emergent adverse event
t_{max}	time to maximum (or peak) serum concentration
ULN	upper limit of normal
Vz_{ss}/F	volume of distribution at steady state
XR	extended-release

1 Protocol Summary

1.1 Synopsis

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Product: Centanafadine (EB-1020)

Protocol No.: 405-201-00154

IND No.: 119361

Protocol Title: A Phase 1, Open-label Trial to Determine the Dose Proportionality and Multiple Dose Pharmacokinetics of Centanafadine Once Daily Extended-release Oral Capsules in Healthy Adults

Protocol Lay Person Short Title: A Study to Test How Different Doses of Centanafadine Given for Multiple Days are Taken up in the Body

Clinical Phase: 1

Planned Treatment/Indication: Attention-deficit/hyperactivity disorder (ADHD)

Trial Rationale:

Lack of a dose proportionality assessment at steady state was identified as a gap in the clinical pharmacology package for centanafadine; as such, this trial is being conducted to provide this information. Dose proportionality and the pharmacokinetics (PK) of multiple doses of a centanafadine once daily (QD) extended-release (XR) capsule will be evaluated using the lowest (164.4 mg), middle (246.6 mg), and highest (328.8 mg) dose strengths to be marketed.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary: To assess the dose proportionality and multiple dose PK of centanafadine QD XR capsules administered in the fasted state to healthy adults.	The following primary PK parameters will be determined for centanafadine after multiple doses: • $C_{ss,max}$ • AUC_{τ} • CL_{ss}/F • Vz_{ss}/F. The following secondary PK parameters will be determined for centanafadine after multiple doses: • t_{max} • $t_{1/2,z}$ • C_{24h}. The same PK parameters (except CL_{ss}/F and Vz_{ss}/F) may be determined for the metabolite, as supported by the data.
Secondary: To evaluate the safety and tolerability of centanafadine QD XR capsules in healthy adults.	Safety: Reported AEs, clinical laboratory tests, vital signs, 12-lead ECGs, and suicidality monitoring (C-SSRS).

AE = adverse event; AUC_{τ} = area under the plasma concentration-time curve over the dosing interval at steady state; C_{24h} = concentration of drug in plasma at 24 hours; CL_{ss}/F = apparent clearance at steady state; $C_{ss,max}$ = maximum (or peak) serum concentration at steady state; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; PK = pharmacokinetics; QD = once daily; $t_{1/2,z}$ = terminal-phase elimination half-life; t_{max} = time to maximum (or peak) serum concentration; Vz_{ss}/F = volume of distribution at steady state; XR = extended-release.

Trial Design:

This is a phase 1, single-center, open-label trial for evaluation of multiple dose PK and dose proportionality of the centanafadine QD XR capsule formulation.

The trial will consist of a screening period (Day −28 to Day −2), check-in (Day −1), an in-clinic treatment and assessment period (Day 1 through discharge on Day 16 or early termination [ET]), and a safety follow-up telephone call on Day 21 (7 [+ 2] days after the last dose of investigational medicinal product [IMP]).

Sixteen healthy adults will be enrolled and administered one 164.4 mg capsule of centanafadine QD XR for 4 days (Days 1 to 4), followed by one 246.6 mg capsule of centanafadine QD XR for 4 days (Days 6 to 9), and then one 328.8 mg capsule of centanafadine QD XR for 4 days (Days 11 to 14). Serial PK samples will be collected over a 48-hour period following dosing on Days 4, 9, and 14 for the determination of centanafadine and metabolite concentrations in plasma. Participants will be discharged on

Day 16 after completion of the safety evaluations and collection of the 48-hour PK sample.

Trial Population:

An appropriate number of participants will be screened in order to enroll and treat up to 16 healthy males and females between 18 and 55 years of age, inclusive. Neither sex will comprise more than 60% of the trial participants. Discontinued participants may be replaced at the sponsor's discretion.

Key Inclusion/Exclusion Criteria:

Male or female participants between 18 and 55 years of age (inclusive), with a body mass index (BMI) between 19.0 to 32.0 kg/m^2 (inclusive), who are in good health as determined by medical history; physical examination; electrocardiogram (ECG); serum/urine chemistry, hematology, and serology tests; and who are able to provide informed consent will be considered for inclusion in the trial. Participants of childbearing potential (POCBP) are required to use 2 different effective and/or highly effective methods of birth control. Any participant who, in the opinion of the investigator, should not participate in the trial will be excluded.

Trial Site(s): This trial will be conducted at 1 trial site in the United States.

Trial Intervention(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Trial interventions are all prespecified IMPs intended to be administered to participants during the conduct of the trial.

The IMP will be provided as 164.4, 246.6, and 328.8 mg to-be-marketed centanafadine QD XR oral capsules. On Days 1 to 4, all participants will receive one 164.4 mg capsule of centanafadine QD XR. On Days 6 to 9, all participants will receive one 246.6 mg capsule of centanafadine QD XR. On Days 11 to 14, all participants will receive one 328.8 mg capsule of centanafadine QD XR.

On serial PK sampling days, the IMP will be administered in the morning with approximately 240 mL of water. No additional water will be permitted from 1 hour prior to IMP administration through 1 hour postdose. Participants will fast for at least 10 hours the night prior to the first day of serial PK sampling for each dose, and no food will be permitted until after 4 hours postdose on the first day of serial PK sampling for each dose. On non-serial PK sampling days, the IMP will be administered in the morning with approximately 240 mL of water at least 1 hour prior to breakfast.

Trial Assessments:

Assessments for Pharmacokinetics: blood sampling for plasma concentrations of centanafadine and metabolite(s).

Assessments for Safety: adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, 12-lead ECGs, and suicidality monitoring (Columbia-Suicide Severity Rating Scale [C-SSRS]).

Screening/Other: medical and medication history; height and weight; serology (human immunodeficiency virus [HIV], hepatitis B surface antigen [HBsAg], and hepatitis C virus); alcohol, drug, and cotinine screen; pregnancy test (all female participants); and follicle-stimulating hormone (FSH) test (postmenopausal female participants only).

Independent Data Monitoring Committee: No

Statistical Methods:

The sample size of 16 enrolled participants was chosen empirically based on practical considerations and variability observed in previous trials using centanafadine QD XR capsules.

Dose proportionality of the primary PK endpoints of maximum (or peak) serum concentration at steady state ($C_{ss,max}$) and area under the plasma concentration-time curve over the dosing interval at steady state (AUC_{τ}) and the secondary PK endpoint of concentration of drug in plasma at 24 hours (C_{24h}) for 164.4 mg, 246.6 mg, and 328.8 mg doses of centanafadine QD XR at steady state (Days 4, 9, and 14, respectively) will be explored using the random intercept power model, with participant as a random effect, using the following equation:

$$\ln(\text{PK parameter}) = \alpha + \beta \ln(\text{dose})$$

where α is the intercept and β is the slope parameter.

All PK parameters will be summarized by treatment and analyte using descriptive statistics.

Trial Duration:

Each participant in this trial is expected to participate in the following periods of the trial (approximate durations listed), for approximately 49 days:

- Eligibility screening period: 27 days (Day −28 to Day −2)
- Check-in: 1 day (Day −1)
- In-clinic treatment and assessment period: 16 days (Day 1 to Day 16)
- Post-treatment follow-up period: 7 (+ 2) days after the last dose of IMP (Day 21)

The trial start is defined as the date the first participant signs their informed consent form (ICF). Overall, the trial duration, from signing of the first participant's ICF to the last participant's final assessment, is expected to be approximately 2 months.

Known and Potential Risks and Benefits:

Data from the completed phase 1, 2, and 3 trials indicate that centanafadine is safe and well tolerated in healthy adults and adults with ADHD. Based on final safety data from the adult phase 2 and 3 trials with the centanafadine sustained-release (SR) tablet administered at total daily doses (TDD) of 200 and 400 mg (with exposures similar to centanafadine QD XR 164.4 and 328.8 mg, respectively), centanafadine was generally safe and well tolerated when administered to adults with ADHD. The most frequently reported treatment-emergent adverse events (TEAEs; ≥ 5%) that occurred at a higher incidence than the placebo group were headache, decreased appetite, nausea, diarrhea, and insomnia.

Rash has also been reported in participants who have been exposed to centanafadine; therefore, rash or other newly acquired, nontraumatic skin eruptions will be considered an adverse event of special interest (AESI) in this trial. The Rash and Skin Eruption AESI Plan will be followed. Considering that rash can be a sign of an allergic reaction, participants will be monitored closely for other symptoms of allergic reaction including shortness of breath, difficulty breathing, swelling of the throat or mouth, swollen face, fever, or swollen lymph nodes.

1.2 Schema

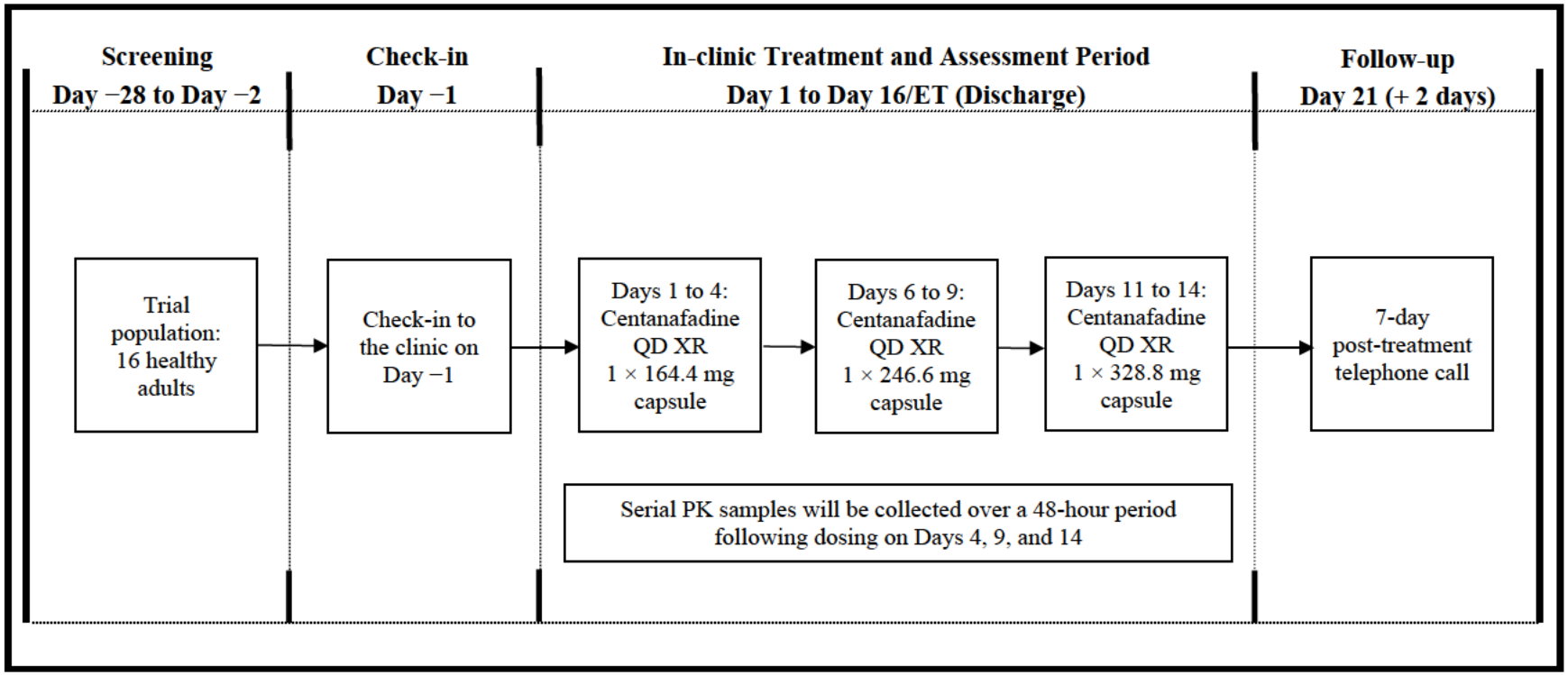


Figure 1.2-1 Trial Design Schematic

ET = early termination; PK = pharmacokinetics; QD = once daily; XR = extended-release.

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments

Period	Screening	Check-in	Treatment															Telephone Follow-up[a]	Notes
Trial Day	−28 to −2	−1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16/ ET	21 (+ 2)	
ENTRANCE/HISTORY																				
Informed consent	X																			Section 10.1.2
Inclusion/ exclusion criteria	X	X																		Section 5.2
Demographics	X																			Section 5.1
Medical history	X																			Section 5.2.2
Height and BMI	X																			Section 5.2.1
Weight	X	X																X		Section 8.6.2
Urine or serum pregnancy test (all females)	X	X																X		Section 10.3
FSH test (postmenopausal females only)	X																			Section 10.3
Hepatitis and HIV screen	X																			Section 5.2.2
Alcohol, drug, and cotinine screen	X	X																		Section 5.2.2
TRIAL RESIDENCY																				
Check-in		X																		Section 4.1
IMP administration			X	X	X	X		X	X	X	X		X	X	X	X				Section 6.1
IMP compliance			X	X	X	X		X	X	X	X		X	X	X	X				Section 6.4
Discharge																		X		Section 4.1
SAFETY																				
Physical examination[b]	X	X					X					X						X		Section 8.6.2
Vital signs	X	X	X[c]			X[c]		X[c]			X[c]		X[c]			X[c]		X		Section 8.6.3

Table 1.3-1 Schedule of Assessments

Period	Screening	Check-in	Treatment															Telephone Follow-up[a]	Notes
Trial Day	−28 to −2	−1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16/ ET	21 (+ 2)	
12-lead ECG[d]	X	X					X					X						X		Section 8.6.4
Laboratory tests (hematology, serum chemistry, and urinalysis)	X	X					X					X						X		Section 8.6.1
C-SSRS	X	X					X					X						X		Section 8.6.5
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.7
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.6
PHARMACOKINETICS																				
Blood draw for PK[e]					X	X	X	X		X	X	X	X		X	X	X	X		Section 8.2.1

BMI = body mass index; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; IMP = investigational medicinal product; PK = pharmacokinetics.

[a]A follow-up telephone call will be made 7 (+ 2) days after the last dose of IMP for trial completers.

[b]A full physical examination will be done at screening; a targeted physical examination will be done at check-in (Day −1), Day 5, Day 10, and discharge (Day 16/ET).

[c]Vital signs will be done predose and 4 hours postdose on Days 1, 4, 6, 9, 11, and 14.

[d]Triplicate ECGs will be performed at check-in (Day −1) only; a single ECG will be performed at screening, Day 5, Day 10, and discharge (Day 16/ET).

[e]Blood samples for PK analysis will be collected on Days 3, 8, and 13: predose; and on Days 4, 9, and 14: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 28, 32, and 48 hours postdose.

2 Introduction

Centanafadine (EB-1020) is being developed for the treatment of ADHD in adults (≥ 18 years of age) and children and adolescents (6 to 17 years of age).

Immediate-release (IR), SR, and XR formulations of centanafadine have been evaluated. As QD dosing is preferred, multiple XR formulations were tested. The final formulation is referred to as the centanafadine QD XR capsule and has been administered in adult phase 1 CCI pediatric phase 1 (405-201-00046), adult proof-of-concept in major depressive disorder (MDD; 405-201-00062), and pediatric pivotal phase 3 (405-201-00016, 405-201-00017, and 405-201-00021) trials.

This trial is being conducted to assess the dose proportionality and PK after multiple doses of a centanafadine QD XR capsule in healthy adults.

Please refer to the Investigator's Brochure (IB) for more detailed information on the chemistry, pharmacology, efficacy, and safety of centanafadine.[1]

2.1 Trial Rationale

Lack of a dose proportionality assessment at steady state was identified as a gap in the clinical pharmacology package for centanafadine; as such, this trial is being conducted to provide this information. Dose proportionality and the PK of multiple doses of a centanafadine QD XR capsule will be evaluated using the lowest (164.4 mg), middle (246.6 mg), and highest (328.8 mg) dose strengths to be marketed.

2.2 Background

Centanafadine is a first-in-class treatment developed for ADHD with inhibitory activity at norepinephrine (NE), dopamine (DA), and serotonin (5-HT) reuptake transporters. In vitro binding assays demonstrated high affinity for NE and moderate affinity for DA and 5-HT transporters, inhibiting reuptake of NE and DA at concentrations similar to or more potent than other ADHD medications.

Centanafadine has been evaluated as IR, SR, and XR formulations over the clinical development program. The SR tablet formulation was administered twice a day in adult clinical pharmacology and adult ADHD efficacy and safety trials. A QD XR capsule formulation of centanafadine was developed to enable QD dosing to support adherence and serve as a pediatric-appropriate formulation with capsules that can be opened, and the contents sprinkled on an appropriate vehicle. This QD XR formulation has been used in adult and pediatric clinical pharmacology trials and pediatric ADHD efficacy and safety

trials and is the intended commercial formulation (referred to as to-be-marketed QD XR capsules).

As of the IB cutoff date of 12 Sep 2023, in total, 2572 participants have received at least 1 dose of centanafadine in completed and ongoing open-label trials including 586 healthy participants, 93 healthy adults who were experienced stimulant users, 16 adults with hepatic or renal impairment, 1051 adults with ADHD, 678 pediatric participants with ADHD, 50 cigarette-smoking adults, and 98 adults with binge-eating disorder.
In addition, 999 additional participants were exposed to centanafadine or placebo in 3 ongoing blinded trials including 451 adolescent participants (13 to 17 years of age) with ADHD (Trial 405-201-00016), 455 child participants (4 to 12 years of age) with ADHD (Trial 405-201-00021), and 93 adults with MDD (Trial 405-201-00062).[1]

2.3 Known and Potential Risks and Benefits

Data from the completed phase 1, 2, and 3 trials indicate that centanafadine is safe and well tolerated in healthy adults and adults with ADHD. Based on final safety data from the adult phase 2 and 3 trials with the centanafadine SR tablet administered at a TDD of 200 and 400 mg (with exposures similar to centanafadine QD XR 164.4 and 328.8 mg, respectively), centanafadine was generally safe and well tolerated when administered to adults with ADHD. The most frequently reported TEAEs (≥ 5%) that occurred at a higher incidence than the placebo group were headache, decreased appetite, nausea, diarrhea, and insomnia.

Rash has also been reported in participants who have been exposed to centanafadine; therefore, rash or other newly acquired, nontraumatic skin eruptions will be considered an AESI in this trial. The Rash and Skin Eruption AESI Plan will be followed. Considering that rash can be a sign of an allergic reaction, participants will be monitored closely for other symptoms of allergic reaction including shortness of breath, difficulty breathing, swelling of the throat or mouth, swollen face, fever, or swollen lymph nodes.

The trial site will receive updated versions of the IB, when available, and the trial site should refer to the most current version as needed.

3 Objectives, Endpoints, and Estimands

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Primary: To assess the dose proportionality and multiple dose PK of centanafadine QD XR capsules administered in the fasted state to healthy adults.	The following primary PK parameters will be determined for centanafadine after multiple doses: • $C_{ss,max}$ • AUC_{τ} • CL_{ss}/F • Vz_{ss}/F. The following secondary PK parameters will be determined for centanafadine after multiple doses: • t_{max} • $t_{1/2,z}$ • C_{24h}. The same PK parameters (except CL_{ss}/F and Vz_{ss}/F) may be determined for the metabolite, as supported by the data.
Secondary: To evaluate the safety and tolerability of centanafadine QD XR capsules in healthy adults.	Safety: Reported AEs, clinical laboratory tests, vital signs, 12-lead ECGs, and suicidality monitoring (C-SSRS).

AE = adverse event; AUC_{τ} = area under the plasma concentration-time curve over the dosing interval at steady state; C_{24h} = concentration of drug in plasma at 24 hours; CL_{ss}/F = apparent clearance at steady state; $C_{ss,max}$ = maximum (or peak) serum concentration at steady state; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; PK = pharmacokinetics; QD = once daily; $t_{1/2,z}$ = terminal-phase elimination half-life; t_{max} = time to maximum (or peak) serum concentration; Vz_{ss}/F = volume of distribution at steady state; XR = extended-release.

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 Type/Design of Trial

This is a phase 1, single-center, open-label trial for evaluation of multiple dose PK and dose proportionality of the centanafadine QD XR capsule formulation.

The trial will consist of a screening period (Day −28 to Day −2), check-in (Day −1), an in-clinic treatment and assessment period (Day 1 through discharge on Day 16 or ET), and a safety follow-up telephone call on Day 21 (7 [+ 2] days after the last dose of IMP).

Sixteen healthy adults will be enrolled and administered one 164.4 mg capsule of centanafadine QD XR for 4 days (Days 1 to 4), followed by one 246.6 mg capsule of centanafadine QD XR for 4 days (Days 6 to 9), and then one 328.8 mg capsule of centanafadine QD XR for 4 days (Days 11 to 14). Serial PK samples will be collected

over a 48-hour period following dosing on Days 4, 9, and 14 for the determination of centanafadine and metabolite concentrations in plasma. Participants will be discharged on Day 16 after completion of the safety evaluations and collection of the 48-hour PK sample.

See Figure 1.2-1 for a schematic of the trial design.

4.2 Scientific Rationale for Trial Design

As described in the Food and Drug Administration (FDA) guidance, for multiple dose studies, QD doses will be administered to achieve steady-state concentrations of the drug.[2] Based on the evaluation of plasma trough concentrations following administration of centanafadine QD XR in the adult phase 1 CCI, steady-state concentrations are reached following 2 days of consecutive QD doses. Serial PK samples will be collected over a 48-hour period following dosing on Days 4, 9, and 14.

4.3 Dosing Rationale

The dose strengths of 164.4 and 328.8 mg centanafadine QD XR represent the lowest and highest dose strengths of centanafadine QD XR to be marketed as single capsules. The dose strength of 246.6 mg centanafadine QD XR represents the middle dose strength of centanafadine QD XR to be marketed as a single capsule. The centanafadine QD XR capsules to be used in this trial are to be sourced from long-term stability of the proposed to-be-marketed capsules and will be the same as those to be marketed commercially, except for color and dose markings.

4.4 Start and End-of-Trial Definitions

The trial start is defined as the first visit of the first participant, which is the date the first participant signs their ICF.

The end-of-trial date is defined as the last date of contact, or the date of the final contact attempt as recorded on the post-treatment follow-up electronic case report form (eCRF) page for the last participant completing or withdrawing from the trial.

4.5 Definition of Trial Participant Completion

The treatment period is defined as the time period during which participants are evaluated for primary and/or secondary objectives of the trial irrespective of whether or not the participant actually takes all doses of the IMP. Participants who are evaluated at the last scheduled visit and complete contact for the follow-up telephone call on Day 21 (7 [+ 2 days] after the last dose of IMP) will be defined as trial completers.

5 Trial Population

An appropriate number of participants will be screened in order to enroll and treat up to 16 healthy males and females between 18 and 55 years of age, inclusive. Neither sex will comprise more than 60% of the trial participants. Discontinued participants may be replaced at the sponsor's discretion.

5.1 Trial Participant Selection and Numbering

All participants will be given a unique subject identifier (ID; site number [3 digits] + subject number ['S' + 5 digits] upon providing consent). The site number will be designated by the sponsor. For each site, the subject number will be given sequentially from S00001.

Demographic information (collection date, year or date of birth, sex at birth, gender identification, childbearing potential, race, ethnicity, country) and medical history will be recorded in the eCRF at the screening visit.

5.2 Eligibility Criteria

Exceptions for eligibility criteria will not be permitted during the trial, neither by the investigator nor by the medical monitor.

5.2.1 Inclusion Criteria

Participants are required to meet the following inclusion criteria when assessed:

1) Male or female participants between 18 and 55 years of age (inclusive).
2) Body mass index from 19.0 to 32.0 kg/m^2 (inclusive).
3) In good health as determined by:
   a) Medical history
   b) Physical examination
   c) Electrocardiogram
   d) Serum/urine chemistry, hematology, and serology tests.
4) Ability to provide written, informed consent prior to the initiation of any trial-related procedures, and ability, in the opinion of the principal investigator, to comply with all the requirements of the trial.

5.2.2 Exclusion Criteria

Participants will be excluded if they meet any of the following exclusion criteria when assessed:

1) Clinically significant abnormality in past medical history, or at the screening physical examination, that in the investigator's or sponsor's opinion may place the participant at risk or interfere with outcome variables including absorption, distribution, metabolism, and excretion of drug. This includes, but is not limited to, history of or concurrent cardiac, hepatic, renal, neurologic, endocrine, gastrointestinal, respiratory, hematologic, and immunologic disease, or cholecystectomy.
2) Consumption of alcohol and/or food and beverages containing caffeine or methylxanthines (eg, coffee, chocolate) within 72 hours prior to dosing.
3) History of drug and/or alcohol abuse within 2 years prior to screening.
4) History of or current hepatitis or AIDS or carriers of HBsAg and/or hepatitis C antibodies (anti-HCV), or HIV antibodies.
5) History of any significant drug allergy or known or suspected hypersensitivity.
6) A positive urine or breath alcohol test and/or urine drug screen for substances of abuse at screening or upon admission to the trial site.
7) Participants having taken an investigational drug within 30 days prior to screening.
8) Any history of significant bleeding or hemorrhagic tendencies.
9) A history of difficulty in donating blood.
10) The donation of blood or plasma within 30 days prior to the first dose of IMP.
11) Use of prescription, over-the-counter, or herbal medications, or vitamin supplements within 14 days prior to the first dose of IMP and antibiotics within 30 days prior to the first dose of IMP. The sponsor may allow exceptions only if the medication's administration is deemed unlikely to impact the PK result.
12) Exposure to any substances known to stimulate hepatic microsomal enzymes within 30 days prior to screening through the end of the trial (eg, occupational exposure to pesticides, organic solvents, etc).
13) Use of tobacco products or daily exposure to second-hand smoke within 2 months prior to the screening visit, urine cotinine concentrations > 200 ng/mL or serum cotinine concentrations > 20 ng/mL at screening or check-in.
14) Participants presenting with, or having a history of, uncontrolled hypertension (supine systolic blood pressure [SBP]> 140 mmHg or diastolic blood pressure [DBP] > 90 mmHg) or symptomatic hypotension, or orthostatic hypotension which is defined as a decrease of ≥ 30 mmHg in SBP or a decrease of ≥ 20 mmHg in DBP after at least 3 minutes of standing compared with the previous supine blood pressure, **OR** development of symptoms. If the standing blood pressure is elevated and exceeds the upper limit (blood pressure > 140/90 mmHg), then the investigator will use clinical judgment to determine if it would be exclusionary.

15) Participants who have a supine pulse rate, after resting for at least 3 minutes, outside the range of 50 to 90 beats per minute.
16) Abnormal ECG findings at screening or check-in, as follows:
    a. QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for male participants or > 470 msec for female participants
    b. QRS interval > 120 msec
    c. PR interval > 200 msec.
17) History of unexplained syncope.
18) History of serious mental disorders, that, in the opinion of the investigator, would exclude the participant from participating in this trial.
19) Participants with no permanent place of residence.
20) Any participant who, in the opinion of the investigator, should not participate in the trial.
21) Previous exposure to centanafadine.
22) Female participants who are breastfeeding.
23) Female participants who have a positive pregnancy test result prior to receiving IMP.
24) Participants of reproductive potential (PORP) / POCBP who do not agree to practice 2 different effective and/or highly effective methods of birth control or remain fully abstinent from sexual activity with the potential for conception, per the guidelines in Section 10.3.
25) Participants who do not agree to refrain from donating sperm or eggs from trial screening through 90 days (for sperm) and 30 days (for eggs) after the last dose of IMP.
26) Any of the following:
    - A significant risk of committing suicide based on history and the investigator's clinical judgment, or routine psychiatric status examination.
    - Current suicidal behavior.
    - Imminent risk of injury to self.
    - Active suicidal ideation as it is evidenced by an answer of "yes" on Questions 4 or 5 (over the last 6 months) on the suicidal ideation section of the Baseline/Screening version of the C-SSRS or at check-in on the "Since Last Visit" form.
    - Any history of suicidal behavior in the past 2 years as detected by the Baseline/Screening version of the C-SSRS or at check-in on the "Since Last Visit" form.

Definitions of reproductive potential and childbearing potential can be found in Section 10.3.

Participants must agree to follow restrictions to medications and lifestyle described in Section 6.6 and Section 5.3, respectively.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Refer to Section 6.1 for fasting requirements and the timing of meals relative to dosing.

5.3.2 Caffeine, Alcohol, and Tobacco

The consumption of alcohol and/or food and beverages containing caffeine or methylxanthines (eg, coffee, chocolate) is prohibited within 72 hours prior to dosing and for the duration of trial participation.

The use of tobacco products or daily exposure to second-hand smoke is prohibited within 2 months prior to the screening visit.

5.3.3 Physical Activity

Participants will not be permitted to participate in strenuous exercise for 72 hours before Day −1 until discharge from the trial site.

Participants will remain either in a seated or semi-recumbent position for the first 4 hours following dosing, except during brief periods when protocol-related procedures need to be performed. Restroom visits must be supervised during the 4 hours postdose and should be brief (< 10 minutes). In addition, during the 4-hour period after oral dosing, the participant's toilet use must be supervised to prevent self-induced emesis resulting in loss of the oral dose. Following the 4-hour postdose period, participants will be allowed to ambulate but should not exercise strenuously.

5.4 Screen Failures

A screen failure is a participant from whom informed consent is obtained and is documented in writing (ie, participant signs an ICF), but who is not randomized or assigned trial intervention(s). Any untoward medical occurrence that occurs in a screen failure is considered a screen failure AE. All screen failure AEs must be recorded in the source document after participant informed consent has been obtained. A screen failure AE must be recorded on an immediately reportable event (IRE) form to the sponsor if the screen failure AE meets the IRE criteria defined in Section 8.7.

If the participant meets the definition of a screen failure in this trial, the following information will be recorded in the eCRF:

- Date of ICF signature
- Visit date (screening visit)

- Demographics (collection date, year or date of birth, sex at birth, gender, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure
- Any screen failure AEs

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Participants with a positive drug or alcohol screen are not eligible to be rescreened for participation in the trial; however, participants excluded for other reasons may be rescreened at any time, at the discretion of the medical monitor, if the exclusion characteristic has changed or resolved. If a participant is rescreened for trial participation and the rescreening is not completed within the original screening window, a new ICF must be signed. Rescreened participants should also be assigned a new subject number for every screening/rescreening event. A participant may not be rescreened more than once.

6 Trial Intervention(s) and Concomitant Therapy

6.1 Trial Intervention(s) Administered

Trial interventions are all prespecified IMPs intended to be administered to participants during the conduct of the trial. No non-investigational medicinal product or auxiliary medicinal product will be specified in this trial.

The IMP will be provided as 164.4, 246.6, and 328.8 mg to-be-marketed centanafadine QD XR oral capsules. On Days 1 to 4, all participants will receive one 164.4 mg capsule of centanafadine QD XR. On Days 6 to 9, all participants will receive one 246.6 mg capsule of centanafadine QD XR. On Days 11 to 14, all participants will receive one 328.8 mg capsule of centanafadine QD XR.

On serial PK sampling days, the IMP will be administered in the morning with approximately 240 mL of water. No additional water will be permitted from 1 hour prior to IMP administration through 1 hour postdose. Participants will fast for at least 10 hours the night prior to the first day of serial PK sampling for each dose, and no food will be permitted until after 4 hours postdose on the first day of serial PK sampling for each dose. On non-serial PK sampling days, the IMP will be administered in the morning with approximately 240 mL of water at least 1 hour prior to breakfast.

For additional information regarding the dosage regimen and treatment period(s), including any follow-up period(s) for each treatment group of the trial, see Section 4.1.

6.2 Management of Trial Intervention(s)

For full details on management of trial intervention(s), please refer to the trial-specific operations manual.

6.2.1 Packaging and Labeling

The IMP will be provided by the sponsor or designated agent to the investigators and the persons designated by the investigator(s) or institution(s). The IMP will be supplied in bottles. Each bottle used in the dosing period will be labeled to clearly disclose the compound ID, trial number, sponsor's name and address, lot number, instructions for use, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to investigators and their designees.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The investigator or designee must maintain an inventory record of IMP received, dispensed, used, and destroyed. Neither the investigator nor any designees may provide IMP to any person not participating in this trial.

6.2.4 Returns and Destruction

The IMP may only be destroyed by the trial site(s) if approved by the sponsor and if the IMP destruction meets all local regulations. The IMP will be destroyed by the clinical trial site following completion and verification of accountability of the IMP by the assigned clinical monitor. The trial site(s) may utilize qualified third-party vendors for IMP destruction. A certificate of destruction should be filed in the trial master file.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, clinical trial participant, medical representative, regulatory agency, partner, or other third party that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a medical device or medicinal product or a falsified, tampered, or diverted product after it is released for distribution.

Examples include, but are not limited to, communications involving:

- Failure/malfunction of a medicinal product or medical device to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product, no safety seal)
- Blister defects (eg, missing, empty blisters)
- Storage temperature discrepancies
- Product defect (eg, odor, chipped, broken, embossing illegible)
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator or designee must record each PQC identified through any means from the receipt of the trial intervention(s) from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including participant dosing.

The investigator or designee must notify the sponsor (or sponsor's designee) within 24 hours of becoming aware of the PQC. CCI [redacted]

Identification of a PQC by the participant should be reported to the site investigator, who should then follow the reporting mechanism above. In these cases, only the investigator's contact information should be provided, not the participant's information.

6.2.5.2 Information Required for Reporting Purposes

- Description of complaint
- Reporter identification (eg, participant, investigator, site, etc)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, coding)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Pictures of complaint sample (if available)
- Availability of complaint sample for return
- Was any participant at risk due to the identified issue?

6.2.5.3 Return Process

Indicate during the report of the PQC if the complaint sample is available for return. If the complaint sample is available for return, the sponsor will provide return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs will be handled by the sponsor.

6.3 Measures to Minimize/Avoid Bias

This is an open-label, non-randomized trial.

6.4 Trial Participant Compliance

The time and dose of each trial intervention administration will be recorded in the eCRF. Information regarding any missed or inappropriately administered doses will also be documented in the eCRF, if possible. All doses of IMP will be administered while the participants are in the clinic; compliance will be ensured by a mouth check during the oral dosing administration of IMP.

6.5 Dose Modification

Not applicable.

6.6 Prior/Concomitant Medications or Therapies

The investigator will record all medications (including, but not limited to, prescription medications, over-the-counter medications, vitamins, herbal remedies, etc) and therapies taken by the participant from 30 days prior to signing of informed consent through the end of the evaluation period (defined as the time period during which participants are evaluated for primary and/or secondary objectives) in the eCRF. The investigator will also record all medications and therapies taken by the participant for treatment of an AE or which caused an AE until the end of the trial (defined as the last date of contact or date of final contact attempt) in the eCRF.

For concomitant medications, the following will be recorded in the eCRF: medication, indication, dose, frequency, route, start date, and end date. For concomitant therapy, the following will be recorded in the eCRF: therapy, indication, start date, and end date.

6.6.1 Prohibited Medications or Therapies

No medications other than the protocol-specific trial IMP may be taken during the trial (with the exception of birth control). The use of prescription, over-the-counter, or herbal medications, or vitamin supplements within 14 days prior to dosing and antibiotics within 30 days prior to dosing is prohibited. The sponsor may allow exceptions only if the medication is unlikely to affect the PK results.

6.7 Intervention After the End of the Trial

Not applicable.

7 Discontinuation of Trial/Treatment and Participant Discontinuation/Withdrawal

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to investigators, institutional review boards (IRBs), and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site Discontinuation

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP). The investigator will notify the sponsor promptly if the investigator or the IRB at the site discontinues participation in the trial.

7.3 Discontinuation of Trial Intervention

Under certain circumstances, it may be necessary for a participant to permanently discontinue trial intervention. If participants discontinue trial intervention, their participation in the trial will be discontinued. Participants who discontinue from the trial should be encouraged to complete all ET and follow-up assessments with ET assessments conducted as soon as possible. See the schedule of assessments (Table 1.3-1) for data to be collected at the time of discontinuation of trial intervention and follow-up and for any further evaluations that need to be completed. If a participant discontinues trial intervention due to an AE, the investigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized.

For each participant who discontinues trial intervention, the main reason for discontinuation will be recorded in the eCRF (refer to Section 7.4.1 Documenting Reasons for Participant Discontinuation/Withdrawal).

Discontinued participants may be replaced at the sponsor's discretion.

7.3.1 Interruption of Trial Intervention

If a participant interrupts treatment, their participation in the trial will be discontinued.

7.3.2 Rechallenge

Not applicable.

7.4 Participant Discontinuation/Withdrawal from the Trial

- A participant may withdraw from the trial at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the trial, if possible, an early discontinuation visit should be conducted, as shown in the schedule of assessments (Table 1.3-1). Also see the schedule of assessments for data to be collected at the time of trial discontinuation and follow-up and for any further evaluations that need to be completed.
- If a participant withdraws consent from the trial, the participant will be permanently discontinued from all trial interventions and the trial.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before the withdrawal of consent.
- If a participant withdraws from the trial, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site trial records.

Complete withdrawal of consent requires a participant's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Contact of the participant by trial site staff, even if only by telephone, to assess the current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the participant's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a participant's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the participant and the integrity of the trial. A participant may initially express their desire to discontinue trial intervention administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3). A participant may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator should determine if the participant can continue participation in the trial. Only participants who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

7.4.1 Documenting Reasons for Participant Discontinuation/Withdrawal

A participant may discontinue trial intervention(s) or withdraw from the trial for the reasons listed below:

- Adverse event
  - Continuing IMP places the participant at undue risk as determined by the investigator (eg, a safety concern that is possibly, probably, or likely related to the IMP)
  - Serious adverse event (SAE)
  - Other potentially IMP-related safety concerns or AEs
- Death

- Lost to follow-up
- Noncompliance with the IMP
- Physician decision
- Pregnancy
- Protocol deviation
- Protocol-specific withdrawal criterion met
- Site terminated by the sponsor
- Withdrawal by participant

7.5 Lost to Follow-up

Participants who cannot be contacted on or before the follow-up telephone call on Day 21 (7 [+ 2 days] after the last dose of IMP), who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the participant, medical records, successful telephone contact with the participant, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the participant by telephone and in the event the site is unable to reach the participant by telephone, the site will attempt to contact the participant via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

If the participant was classified as "lost to follow-up," the following information will be recorded in the eCRF: "Date of final contact attempt" and "Contact method."

8 Trial Procedures

The expected duration of trial participation for each participant will be approximately 49 days, consisting of a screening period (Day −28 to Day −2), check-in (Day −1), an in-clinic treatment and assessment period (Day 1 through discharge on Day 16 or ET), and a safety follow-up telephone call on Day 21 (7 [+ 2] days after the last dose of IMP).

The overall trial duration, from signing of the first participant's ICF to the last participant's final assessment, is expected to be approximately 2 months.

The assessments to be conducted during the trial are summarized in Table 1.3-1.

8.1 Efficacy Assessments

Not applicable.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Blood Samples

Blood samples for PK analysis will be collected at the time points as shown in the schedule of assessments (Table 1.3-1). These samples should be collected within ± 3 minutes of the nominal time. Predose samples should be collected within 60 minutes before administration of the IMP.

When vital signs or ECGs are scheduled at the same nominal time as PK sample collections, vital signs should be measured and ECGs should be performed before PK samples are collected. The actual date and time of the PK sample collection will be recorded in the eCRF.

Blood samples (4 mL) will be collected in vacutainers containing dipotassium ethylenediaminetetraacetic acid (K_2EDTA) and processed into plasma to determine the concentrations of centanafadine and metabolite(s). Metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C, unless otherwise instructed in the trial-specific laboratory manual.

All PK samples will be shipped to the bioanalytical laboratory. Additional information will be provided in the trial-specific laboratory manual.

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8.6 Safety Assessments

Safety assessments in this trial include AEs, clinical laboratory tests, physical examinations, vital signs, 12-lead ECGs, and suicidality monitoring (C-SSRS).

Vital signs should be measured and ECGs should be performed before any blood samples are collected, where applicable.

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.7.

8.6.1 Clinical Laboratory Assessments

Clinical laboratory samples will be collected at the time points described in the schedule of assessments (Table 1.3-1) to perform the clinical laboratory assessments described in Section 10.2.

Refer to the trial-specific laboratory manual for information on how to identify laboratory values outside of normal reference ranges and for instructions on how to assess for potential clinical significance. The total volume of blood to be collected during the trial will be documented in the ICF.

8.6.2 Physical Examination

Physical examinations will be performed at the time points described in the schedule of assessments (Table 1.3-1).

A complete physical examination will be performed at screening and will include height, weight, and calculation of BMI as well as an assessment of the head, eyes, ears, nose, and throat; thorax; abdomen; skin and mucosae; neurological system; and extremities.

A targeted physical examination will be performed at all other scheduled time points, or will be conducted as necessary in response to reported AEs.

Any abnormalities that are observed after the screening period and are considered by the investigator to be clinically significant are to be recorded as AEs on the source documents and in the eCRF.

Whenever possible, the same individual should perform all physical examinations for any individual participant throughout the course of the trial. Individuals performing the physical examination must be permitted to do so by local regulations, must be listed on

the FDA Form 1572 as principal investigator or subinvestigator, and must be listed on the site delegation of authority form as performing this function.

8.6.3 Vital Signs

Vital signs (including blood pressure, heart rate, and body temperature) will be collected at the time points described in the schedule of assessments (Table 1.3-1).

Blood pressure and heart rate measurements will be made in the supine and standing positions after the participant has been in each position for at least 3 minutes. The supine measurements will be performed first followed by the standing measurements.

Participants' vital signs should be monitored and assessed for potential clinical significance. Any post-screening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs in the eCRF.

8.6.4 Electrocardiogram

Electrocardiograms will be performed in the supine position at the time points described in the schedule of assessments (Table 1.3-1). Triplicate ECGs will be performed at check-in (Day −1) only; in an instance where 1 or more of the ECG readings are exclusionary, then they will be included in the average of 3 ECG readings and evaluated for eligibility. A single ECG will be performed at all other scheduled time points.

Participants' ECGs should be monitored and assessed for potential clinical significance. Any post-screening abnormalities considered by the investigator to be clinically significant are to be recorded as AEs in the eCRF.

The ECG data will be captured manually in the eCRF. The principal investigator or other qualified individual delegated to do so must review, sign, and date each ECG reading. The reviewer must be listed on the FDA Form 1572 and the site delegation of responsibility form.

8.6.5 Suicidality Monitoring

Suicidality monitoring will occur at the time points described in the schedule of assessments (Table 1.3-1).

Suicidality will be monitored during the trial using the C-SSRS. The C-SSRS is a semi-structured interview that captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The interview includes definitions and suggested questions to solicit the type of information needed to determine if a suicide related thought or behavior has occurred. The interview and rating for the C-SSRS must be completed by a licensed clinician or designee who has completed

the required rater training to complete this assessment and who has been approved by the sponsor to administer this assessment. Documentation of the training should be maintained in the trial site's files.

The "Baseline/Screening" Version of the C-SSRS will be completed at the screening visit and the "Since Last Visit" version of the C-SSRS will be completed at all other time points. There are required items to be completed, potential additional items if there is a positive response to a required item, and items for suicide/suicide behavior present during the interview. The C-SSRS uses dichotomous scales (ie, yes or no), Likert scales, and text or narrative to further describe the thoughts or behaviors.

8.7 Adverse Events

8.7.1 Definitions

Trial interventions are all pre-specified IMPs intended to be administered to the participants during the conduct of the trial.

Adverse Event: an AE is defined as any untoward medical occurrence in a clinical trial participant administered a trial intervention, and which does not necessarily have a causal relationship with this intervention. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse reaction is any untoward and unintended response to a trial intervention related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the trial intervention caused the AE. For the purpose of Investigational New Drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the trial intervention and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality.

Treatment-emergent AEs are defined as AEs with an onset date on or after the start of IMP treatment. In more detail, TEAEs are all AEs which started after the start of IMP; or if the event was continuous from baseline and was worsening, serious, IMP-related, or resulted in death, discontinuation, interruption, or reduction of the IMP.

A serious adverse event includes any event that results in any of the following outcomes:

- Death
- Life-threatening, ie, the participant was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the participant, and may require medical or surgical intervention to prevent one of the outcomes listed above, eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Adverse Events of Special Interest: a noteworthy event for the particular IMP or class of products that a sponsor may wish to monitor carefully. All AESIs are to be reported as IREs.

Immediately Reportable Event:

- Any SAE.
- Any AESIs (see Section 8.7.5)
- Potential serious hepatotoxicity (see Section 8.7.7).
- Any AE related to occupational exposure (eg, an investigator getting a skin rash after exposure to a medication). Non-participant AEs would not be recorded on the eCRF form but must be recorded on an IRE form to the sponsor.
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, pregnancy of a trial participant will mandate trial intervention discontinuation and pregnancy of a participant or a participant's partner must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be documented on the AE eCRF if the pregnancy occurs in a trial participant and there is an abnormality or complication (see Section 10.3).

Clinical Laboratory Test Value Changes: it is the investigator's responsibility to review the results of laboratory tests for each individual participant as they become available. This review will be documented by the investigator's dated signature on the laboratory report. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator (participant is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation and/or fulfills a seriousness criterion, this is considered an AE.

Severity: AEs will be graded on a 3-point scale and reported as indicated in the eCRF. The severity of an adverse experience is defined as follows:

1 = Mild:	discomfort noticed, but no disruption to daily activity.
2 = Moderate:	discomfort sufficient to reduce or affect normal daily activity.
3 = Severe:	inability to work or perform normal daily activity.

IMP Causality: assessment of a causal relationship of an AE to the use of the IMP is defined as follows:

Related:	there is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	there is no temporal or causal relationship between the IMP and the AE.

8.7.2 Eliciting and Reporting Adverse Events

The investigator will regularly assess participants for the occurrence of AEs. To avoid bias in eliciting AEs, participants should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the participant must be recorded on the source documents and in the eCRF provided by the sponsor. Adverse event collection will begin after a participant signs the ICF, and will continue until the participant's last scheduled contact unless the AE must be followed further. All screen failure AEs will be recorded as described in Section 5.4.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

Medical or surgical procedures (eg, endoscopy, appendectomy) should not be reported as AEs; however, the condition that led to the procedure may be reported as an AE.

If a reported AE undergoes a change or worsening in severity, seriousness, or toxicity, it should be reported as a new AE in the eCRF.

In addition, the sponsor must be notified immediately by telephone, fax, or e-mail of any IREs according to the procedure outlined below, in Section 8.7.3. Special attention should be paid to recording hospitalization and concomitant medications.

The AE, start date, end date (if possible, start date and time, end date and time), seriousness, severity, relationship to the IMP (causality), action taken with the IMP, and outcome will be recorded on the source documents and in the eCRF.

Note: the start time should be recorded in the event an AE such as vomiting occurs. When capturing the start/end time, at a minimum, the hour should be captured in the event it is difficult to specify in hours and minutes.

Regarding SAE, relationship to, and action taken with trial intervention(s) other than IMP will also be evaluated per each intervention. These evaluations will be recorded in the source documents and in the eCRF and will be reported using the IRE form (see Section 8.7.3).

8.7.3 Immediately Reportable Events

The investigator must immediately report (within 24 hours), using an IRE form, after the investigator or site personnel become aware of any IRE (SAE, AE related to occupational exposure, AESI, potential serious hepatotoxicity, or confirmed pregnancy), by telephone, fax, or e-mail to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE eCRF). Participant confidentiality must be protected and contact information such as name, address, phone number, or any other protected health information as determined by applicable local regulations must be redacted when forwarding Safety Information and supporting documentation. Details regarding the follow-up of IREs are included in Section 8.7.9.2.

8.7.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.7.5 Adverse Events of Special Interest

Newly acquired, nontraumatic skin eruptions are considered AESIs. The following examples would not be considered AESIs: contact dermatitis, insect bites and stings, poison plant intoxication (eg, poison ivy), skin reactions to ECG electrodes or similar adhesive tape, or chemical or thermal burns. Some examples of AESIs should include, but are not limited to, newly acquired maculopapular, macular, papular, papulosquamous, urticarial, acneiform, mucosal, cutaneous, mucocutaneous, vesicular, pustular, bullous, squamous, exfoliative, pruritic or non-pruritic, erythematous, exanthematous also known as morbilliform rashes or skin eruptions which are localized or generalized, regardless of severity (mild, moderate, severe) or seriousness (ie, nonserious lesions are also eligible).

Rash/Skin Eruption AESI Workup Instructions are in place to monitor AESIs. The instructions explain the whole process, providing step-by-step instructions, and comprise the following basic components:

- AESI Form
- IRE Form
- Remote Electronic Virtual Assessment Application to capture and securely transmit the skin eruption photographs
- Clinical research site personnel
- Central dermatologist
- Local dermatologist or teledermatology service
- Sponsor medical monitor and Clinical Research Organization (CRO) medical monitor
- Sponsor pharmacovigilance representatives
- Stopping rules for the IMP in case there is an AESI
- Blood work including the steps in bullous eruption or potential drug reaction with eosinophilia and systemic symptoms / drug-induced hypersensitivity syndrome scenarios
- Biopsy-related instructions when applicable

In addition, skin checks must be conducted during each physical examination.

The trial site will have a local designated dermatologist available for consultation as needed for these AESIs.

All AESIs should be reported as IREs (see Section 8.7.3).

8.7.6 Abuse Potential Monitoring Process, Events Subject to Additional Monitoring, and Medication Handling Irregularities

A key objective of the Abuse Potential Monitoring Process (APMP) is to monitor for instances of abuse or diversion of the IMP and other psychoactive substances. In addition to monitoring for irregularities in medication handling, AEs that may be suggestive of a developing abuse issue will also receive special attention. As part of the APMP, medication handling irregularities (MHIs) must be reported, and AEs related to abuse potential and AEs involving MHIs must be reported as Events Subject to Additional Monitoring (ESAMs) with detailed narratives. Investigators and site staff at the trial site will be trained on reporting potentially abuse-related AEs (eg, recording a description of the event in the participant's own words in the source documents as well as the eCRF, in addition to the clinical term, and to be aware that a participant's report may encompass more than one event and that these should be recorded separately). The investigators will be provided with examples of potentially abuse-related AEs and trained on how to handle such events (eg, additional monitoring).[3] While the investigators will be provided with examples of AE terms as a guide during trial conduct, the analysis of potentially abuse-related AEs will be based on a search of all Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, all verbatim terms, and any open text fields within the AE data to identify text strings suggestive of abuse potential, in line with the 2017 FDA guidance (Assessment of Abuse Potential of Drugs).

Refer to the separate APMP documentation for complete details on MHIs and ESAMs, including documenting and reporting procedures, examples of potentially abuse-related AE terms that meet the criteria for ESAM reporting, and guidance for the training of investigators and trial site staff.

8.7.7 Potential Serious Hepatotoxicity

For a participant who experiences an elevation in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) that is ≥ 3 times the upper limit of normal (ULN), a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form with all values listed and report as an AE in the eCRF.

8.7.8 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.7.9 Follow-up of Adverse Events

8.7.9.1 Follow-up of Nonserious Adverse Events

With the exception of screen failures, nonserious AEs that are identified at any time during the trial must be recorded in the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing in the eCRF. For any AE having been identified throughout the trial, additional relevant medical history information may be requested by the sponsor during analysis of the event, to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation). All screen failure AEs will be recorded as described in Section 5.4.

8.7.9.2 Follow-up of Immediately Reportable Events

This trial requires that participants be actively monitored for IREs up to 7 (+ 2) days after the last trial intervention is administered.

Immediately reportable events that are **identified or ongoing at the last scheduled contact** must be recorded as such in the AE eCRF and on the IRE form. If updated information (eg, resolved status) on the IRE status becomes available after a participant's last scheduled contact (up to the last in-clinic visit for the entire trial), this must be reported to the sponsor and recorded in the AE eCRF and on the IRE form, according to the appropriate reporting procedures described in Section 8.7.3.

It is expected that the investigator will provide or arrange appropriate supportive care for the participant and will provide prompt updates on the participant's status to the sponsor. The investigator will follow the IREs until:

- The events are resolved,
- The events have stabilized,
- The participant is lost to follow-up, or
- The participant has died.

Resolution means that the participant has returned to the baseline state of health and stabilized means that the investigator does not expect any further improvement or worsening of the participant's condition. The investigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for participants that become pregnant or for pregnant partners of trial participants.

8.7.9.3 Follow-up and Reporting of Immediately Reportable Events Occurring After Last Scheduled Contact

Any new IREs reported to the investigator that occur after the last scheduled contact and are determined by the investigator to be reasonably associated with the use of the trial intervention(s), should be reported to the sponsor according to the procedures outlined in Section 8.7.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period. Any significant follow-up information should continue to be reported to the sponsor until the events are resolved or stabilized, or the participant is lost to follow-up or has died.

8.8 Treatment of Overdose

For treatment of overdoses, please refer to the centanafadine IB section for overdose.[1]

8.9 Participant Assessments

Not applicable.

8.10 Other Assessments

Not applicable.

9 Statistical Considerations

9.1 Sample Size

The sample size of 16 enrolled participants was chosen empirically based on practical considerations and variability observed in previous trials using centanafadine QD XR capsules.

9.2 Datasets for Analysis

The safety dataset includes all participants who are administered at least one dose of IMP.

The PK dataset includes all participants who are administered at least one dose of IMP and have evaluable plasma concentration data and PK parameters.

9.3 Handling of Missing Data for Primary Endpoint Analysis

No data imputation will be performed for missing PK data in this trial. The handling of concentrations below the lower limit quantitation will be according to the sponsor's data handling process.

9.4 Statistical Analyses

9.4.1 Primary Endpoints Analysis

Dose proportionality of the $C_{ss,max}$ and AUC_{τ} values for 164.4 mg, 246.6 mg, and 328.8 mg doses of centanafadine QD XR at steady state (Days 4, 9, and 14, respectively) will be explored using the random intercept power model, with participant as a random effect, using the following equation:

$$\ln (\text{PK parameter}) = \alpha + \beta \ln (\text{dose})$$

where α is the intercept and β is the slope parameter.

Details of the analysis will be described in the statistical analysis plan (SAP).

See Section 9.4.5.2 for analyses of all of the primary PK endpoints.

9.4.2 Secondary Endpoints Analysis

For the dose proportionality analysis of C_{24h}, the same random intercept power model as for the primary endpoint analysis will be used. Details of the analysis will be described in the SAP.

For the plasma concentration and PK parameter analyses for all of the PK endpoints, see Section 9.4.5.2. For the safety analyses, see Section 9.4.4.

9.4.3 Control of Experiment-wise Type 1 Error

Not applicable.

9.4.4 Safety Analyses

9.4.4.1 Adverse Events

All AEs will be coded by system organ class and MedDRA preferred term. The incidence of the following events will be summarized by centanafadine dose:

- TEAEs
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- TEAEs causally related to the IMP
- AESIs

9.4.4.2 Clinical Laboratory Data

Clinical laboratory test results (observed and change from baseline data) will be summarized by visit. The incidence of potentially clinically relevant clinical laboratory test results will also be summarized. All clinical laboratory test results will also be presented in a listing.

9.4.4.3 Physical Examination and Vital Signs Data

Physical examination data will be presented in a listing.

Vital signs results (observed and change from baseline data) will be summarized by centanafadine dose. The incidence of potentially clinically relevant vital signs results will also be summarized by centanafadine dose. All vital signs results will also be presented in a listing.

9.4.4.4 Electrocardiogram Data

Electrocardiogram results at baseline will be summarized for all participants. Baseline will be determined by the average of the triplicate ECGs.

The ECG results (observed and change from baseline data) will be summarized by visit. The incidence of potentially clinically relevant ECG results will also be summarized. All ECG results will also be presented in a listing.

9.4.4.5 Other Safety Data

9.4.4.5.1 Suicidality

Suicidality will be monitored during the trial using the C-SSRS. The incidence of suicidal behavior, suicidal ideation, and suicidality will be summarized by visit. The analysis details will be provided in the SAP.

9.4.5 Other Analyses

9.4.5.1 Analysis of Demographic and Baseline Characteristics

Baseline demographic characteristics including age, race, ethnicity, sex at birth, weight, height, and BMI for the enrolled participants will be summarized by descriptive statistics (frequency, mean, median, standard deviation, maximum, minimum, and percentage when applicable).

9.4.5.2 Pharmacokinetic Analyses

Individual plasma concentrations of centanafadine and its metabolite(s) will be summarized by analyte, treatment, and time point using descriptive statistics.
A noncompartmental analysis will be performed to estimate the PK parameters of centanafadine and its metabolite(s). All PK parameters will be summarized by treatment and analyte using descriptive statistics (mean, median, standard deviation, percent coefficient of variation [%CV], minimum, maximum, and geometric mean). The time to maximum (or peak) serum concentration (t_{max}) will be summarized by median and range.

9.5 Interim Analysis

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, FDA regulations, applicable International Council for Harmonisation (ICH) GCP guidance, international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval/favorable opinion by an IRB according to regional requirements, and the investigator will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the eCRF, IRE, and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting the privacy of trial participants. To this end, a subject ID will be used to identify each participant.

Financial aspects, participant insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the investigator.

Diversity and inclusion are essential in all aspects of clinical trials to generate evidence-based approaches that are generalizable and applicable to the populations that are most likely to benefit from the medications or products being studied. Clinical trials must be inclusive of underrepresented racial and ethnic populations and other minority groups to account for diverse lived experiences. Otsuka is committed to promoting an inclusive environment that engages a diversity of participants, sites, investigators, and site staff in the execution of its clinical trials.

10.1.2 Informed Consent

Informed consent will be freely obtained from all participants. The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH GCP guidelines and local regulatory requirements. The investigator will ensure that the sponsor reviews and authorizes any written site-specific ICF used in the trial before submission to the IRB.

Investigators may discuss trial availability and the possibility for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential participants are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the participant by the investigator (or a qualified designee), and it has been documented that the participant has had the opportunity to ask questions and have those questions answered, the IRB-approved paper ICF will be signed and dated by both the participant and the person obtaining consent (investigator or designee), as well as by any other parties required by the IRB. The participant will receive a copy of the signed ICF; the original shall be kept on file by the investigator. Participants may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the participants, so that they can make a knowledgeable and voluntary decision on continued trial participation. If a partner of a trial participant becomes pregnant during the course of the trial, the nonparticipant partner may be asked to sign an ICF in order to collect additional information regarding the nonparticipant partner and fetus.

10.1.3 Recruitment Strategy

Methods for participant recruitment may include but are not limited to media (ie, television, radio, and newspaper), physician referrals, press releases, fliers, random mailings, cold calls, and the internet. The methods will be selected before the start of the trial and may be added as the trial progresses.

10.1.4 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Participant confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All trial intervention(s), participant bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Participants will be identified only by their unique subject ID in the eCRF. If further participant identification is required, participants' full names may be made known to a regulatory agency or other authorized officials, if necessary, subject to local regulations.

The contract between the sponsor and the trial site specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

If trial intervention monitoring will be conducted by an innovative application, the retention and use of images and data will be in accordance with the terms of the master service agreement with the vendor.

10.1.5 Quality Control and Quality Assurance

10.1.5.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, the applicable ICH GCP guidance, and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.5.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, trial intervention supply, the presence of required documents, the informed consent process, site operations, delegation of authority and training, and a review of the eCRF with source documents, as applicable. The investigator will agree to cooperate and participate with audits.

Regulatory authorities may inspect the investigator site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.6 Protocol Deviations

In the event of a significant/major deviation from the protocol due to an emergency, accident, or mistake (eg, violation of the informed consent process, trial intervention dispensing or participant dosing error, treatment assignment error, participant enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the participant's continuation in the trial. This decision will be documented by the investigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the eCRF along with the start date and details of the deviation.

10.1.7 Records Management

10.1.7.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, progress notes, paper-based assessments and scales, and recorded data from automated instruments or applications. All source documents pertaining to this trial will be maintained by the investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, participant confidentiality must be maintained in accordance with local regulatory requirements.

10.1.7.2 Data Collection

During each participant's visit to the site, an investigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised ICFs;
- Documentation of the investigator's decision to enroll the participant into the trial, the review of all inclusion/exclusion criteria prior to trial intervention administration, and confirmation of the participant's actual participation in the trial;
- Documentation of baseline and demographic characteristics (eg, age, weight, BMI, sex at birth, gender, race, ethnicity)

- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General participant status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator's assessment of relationship to trial intervention must also be recorded;
- Any changes in concomitant medications or dosages;
- A general reference to the procedures completed, including dosing and trial intervention compliance;
- The signature (or initials) and date of the investigator (or designee) who made an entry in the medical record;
- The time of last food eaten prior to IMP dosing, the time of the meal provided on dosing days, and the actual time of IMP dosing and PK sample collection will all be recorded in the eCRF.

In addition, any contact with the participant via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Information from medical records and other source documents will be entered by investigative site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is compliant with 21 Code of Federal Regulations Part 11. Changes to the data will be captured by an automatic audit trail in the EDC system.

Electronic data not entered on the eCRF will be reconciled using key data fields by the sponsor or the CRO with the eCRF data to ensure consistency.

10.1.7.3 File Management at the Trial Site

The investigator will ensure that the trial site file is maintained in accordance with applicable ICH GCP guidance and as required by applicable local regulations. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

10.1.7.4 Records Retention at the Trial Site

The FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- A period of at least 2 years after the date on which a New Drug Application (NDA) is approved by the FDA;
- A period of 2 years after the sponsor has notified the FDA that investigation with this drug is discontinued.

The investigator must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to collect such records. The investigator will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities. If the investigator withdraws from the trial (eg, due to relocation or retirement), all trial-related records should be transferred to a mutually agreed-upon designee within a sponsor-specified timeframe. Notice of such transfer will be given to the sponsor in writing.

10.1.7.5 Dissemination of Clinical Trial Data

Trial data will be disseminated as required by regulation.

10.1.7.6 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on the International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to the ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other personnel involved in the conduct of the trial who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other personnel involved in the conduct of the trial consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology:	Serum Chemistry:
Erythrocytes	Alkaline phosphatase
Hematocrit	ALT
Hemoglobin	AST
Leukocytes count with differential	Bilirubin, total
Mean corpuscular hemoglobin concentration	Blood urea nitrogen
Mean corpuscular volume	Calcium
Platelets	Carbon dioxide
	Chloride
Urinalysis:	Cholesterol, total
Bilirubin	Creatine phosphokinase
Color	Creatinine
Glucose	Gamma glutamyl transferase
Ketones	Glucose
Microscopic analysis, white blood cell/red blood cell counts per high powered field, casts, crystals, squamous cells	Lactic dehydrogenase
	Potassium
	Protein, total
Occult blood	Sodium
pH	Triglycerides
Protein	
Specific gravity	Drug Screen (all items in urine except where noted):
Specimen appearance	Alcohol (breath or urine)
Urobilinogen	Amphetamines
	Barbiturates
	Benzodiazepines
	Cannabinoids
	Cocaine
	Cotinine (urine or serum)
	Methadone
	Opiates
	Phencyclidine
	Propoxyphene
	Additional Tests:
	FSH for postmenopausal females
	Urine or serum pregnancy test for all females
	Viral serology (HIV, HBsAg, anti-HCV)

ALT = alanine aminotransferase; anti-HCV = hepatitis C antibodies; AST = aspartate aminotransferase; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus.

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

DEFINITIONS:

Participants of reproductive potential (PORP) are defined as those participants who have reached onset of menarche or clear onset of puberty (Tanner stage B3 or stage G3) and who are not documented as sterile (eg, have had a bilateral orchiectomy or have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

Participants of childbearing potential (POCBP) are those for whom menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months).

CONTRACEPTIVE GUIDANCE:

For PORP and POCBP and their partners who are sexually active, there must be a documented agreement that the participant and their partner will take measures (ie, 2 different effective and/or highly effective methods of birth control per the table below or remain abstinent from sexual activity with the potential for conception) to prevent pregnancy during the course of the trial and for 90 days for males and 30 days for females after the last trial intervention administration.

The contraceptive method(s) will be documented in the eCRF. All PORP must also agree not to donate sperm or eggs from trial screening through 90 days for sperm and 30 days for eggs after the last trial intervention administration.

CONTRACEPTIVES[a] ALLOWED DURING THE TRIAL INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the POCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] – Oral – Intravaginal – Transdermal – Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation[c] – Oral – Injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from sexual activity with the potential for conception during the entire period of risk associated with the trial intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the trial and the preferred and usual lifestyle of the participant.*
Effective Methods[d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
Progestogen-only oral hormonal contraception where inhibition of ovulation isn't the primary mode of action
External or internal condom with or without spermicide
Cervical cap, diaphragm, or sponge with spermicide
A combination of external condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]

a) Contraceptive use by PORP should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c) External condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d) Considered effective, but not highly effective - failure rate of ≥ 1% per year.

NOTE: periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. External condom and internal condom should not be used together (due to risk of failure from friction).

PROCESSES:

Before enrolling participants in this clinical trial, investigators must review the following information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, PORP and POCBP and their partners must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Participants must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for human chorionic gonadotropin (hCG) will be performed at screening, check-in (Day −1), and discharge (Day 16/ET) on all POCBP. If a urine test is performed and is positive, the investigator will follow-up with a confirmatory serum test.

During the trial, all POCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). All PORP must also be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle) with their child.

If a POCBP is suspected to be pregnant before receiving trial intervention(s), the intervention administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the participant must not receive the trial intervention(s) and must not be enrolled in the trial. If pregnancy is suspected while the participant is taking trial intervention(s), the intervention(s) must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the trial intervention(s) will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety) and the participant will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with trial intervention exposure during the trial and for at least 30 days after the last trial intervention administration for female participants and 90 days after the last trial intervention administration for female partners of male participants, and record the event on the IRE form and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the participant unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Protocol Amendments

The investigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "non-substantial" amendments, investigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Non-substantial amendments are defined as having no effect on the safety of participants, conduct or management of the trial, trial design, or the quality or safety of intervention(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to participants should be implemented immediately after agreement by the sponsor and investigator, followed by IRB notification within local applicable timelines. The sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the participant, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from currently enrolled participants in the trial before the amendment-specified changes in the trial are implemented.

10.4.1 Protocol Amendment(s)

Not applicable.

11 References

1 Otsuka Pharmaceutical Development and Commercialization. Centanafadine (EB-1020) Investigator's Brochure, Edition 13. Otsuka Report, issued 10 Jan 2024.

2 US Food and Drug Administration Guidance for Industry. Bioavailability studies submitted in NDAs or INDs — general considerations guidance for industry. www.fda.gov/media/121311/download. Published April 2022. Accessed 06 May 2024.

3 FDA Center for Drug Evaluation and Research. Guidance for Industry: Assessment of Abuse Potential of Drugs. January 2017. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf.

Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational medicinal product, centanafadine, any other trial interventions or concurrent medications, the efficacy and safety parameters, and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where centanafadine will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on the eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for participants screened or enrolled in the trial.

I agree to await Health Authority (HA) and IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to participants, I will implement the amendment immediately, and provide the information to the HA and IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all participants with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____	_____
Principal Investigator Print Name	Signature	Date

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SIGNATURE PAGE

Document Name: 405-201-00154 Protocol

Document Number: 1000301269

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:min) - UTC timezone
PPD	Biostatistics Approval	17-Jul-2024 21:04:28
PPD	Clinical Approval	18-Jul-2024 20:24:55
PPD	Clinical Pharmacology Approval	17-Jul-2024 21:44:18